this reduction in the intimal thickening would reduce occurrence of restenosis from approximately 30% of patients to less than 10%.--

## Remarks

### Response to Restriction Requirement

A petition for supervisory review of the restriction requirement imposed June 11, 2002, made final in the office action mailed September 6, 2002, has been filed. The elected group of claims are directed to Group I (claims 1-12) for methods of inhibiting stenosis or restenosis with anti-Mac-1 antibodies.

### Title

It is understood that the title is viewed as non-descriptive. However, applicants prefer to defer the issue of what the title should reflect as the claimed invention until the petition issue has been resolved.

### Rejection Under 35 U.S.C. § 112, first paragraph

**I.** Claims 1-9, and 11-12 were rejected under 35 U.S.C. § 112, first paragraph, as not enabled. Applicants respectfully traverse this rejection.

*a. The Legal Requirements*

35 U.S.C. §112 requires that the specification be enabling to a person skilled in the art. *See Rengo Co. Ltd. v. Molins Mach. Col.*, 657 F.2d 535, 549 (3d Cir. 1980) (every description will rely to some extent on the reader's knowledge of the terms, concepts, and depictions it embodies). The person skilled in the art is presumed to know all the art which is generally and

reasonably available and has the knowledge of where to search out information. *In re Howarth*, 654 F.2d 103, 106 (CCPA 1981). The sufficiency of the specification on how to make and use the invention must be accepted unless the Patent Office provides adequate reason to doubt the accuracy of the disclosure. If the Patent Office doubts the sufficiency, then the burden shifts to the applicant to demonstrate the enablement of the disclosure by suitable evidence. Additional evidence, such as additional exemplary data and literature support, is available to substantiate any assertions that the enablement is in fact commensurate with the scope of protection sought and to respond to any demands based thereon for proof. *In re Marzocchi*, 439 F.2d 220, 223 (CCPA 1971); *Ex parte Obukowicz*, 27 USPQ2d 1063, 1066-67 (Bd. Pat. App. & Int'f 1992).

The test under 37 C.F.R. §112 is clear - the specification must be enabling to those skilled in the art **at the time the application is filed**, without undue experimentation.

> The determination of what constitutes undue experimentation in a given case requires application of standard of reasonableness, having due regard for nature of invention and state of the art. *Ansul Co. v. Uniroyal, Inc.* supra. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable determination of how to practice desired embodiment of invention claimed. *In re Rainer*, 52 CCPA 1593, 347 F.2d 574, 146 USPQ 218 (1965). Also see In re Colianni, supra.
>
> *Ex parte Jackson*, 217 USPQ 804 at 807 (Bd. App. 1982).

See also *In re Wands*, 8 USPQ 1400 at 1406-1407 (Fed. Cir.), stating that it does not constitute undue experimentation even when screening of large numbers is required, if there is a relatively low percentage of positives. Such a determination must be made in view of the circumstances of each case and cannot be made solely by reference to a particular numerical cutoff. *In re Wands* at 1407. Quoting from *Utter v. Hiraga*, 845F.2d 993, 998, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988), "A specification may, within the meaning of 35 U.S.C. §112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses". Quoting from *in re Robins*, 429 F.2d 452, 456-457, 166 USPQ 552, 555 (CCPA 1970), "[R]epresentative samples are not required by the statute and are not an end in themselves".

The standard for making a rejection based on 35 U.S.C. § 112, first paragraph is articulated in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) (see also MPEP § 2164.01 and 2164.04). Initially, the Patent Office must accept the objective truth of statements made in the specification. If such statements are to be called into question, the Patent Office is burdened with providing evidence or convincing argument why those of skill in the art would doubt the statements (*In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971)). Applicants assert that this burden has not been met.

Furthermore, in a recent decision by the CAFC, the court ruled that in the event that the specification described and enabled various possible species and provided specific information on methods of use, description of one species would enable one of ordinary skill to practice the method pertaining to the genus. *Amgen Inc. v. Hoescht Marion Roussel, Inc.* 01-1191, -1218 - (C.A.F.C.)

*b. The Application contains supporting data and Additional data is been provided*

Data has been submitted in the application and subsequently showing the efficacy of one of these inhibitors, antibodies to Mac-1. See the examples at pages 22-23 of the application as filed, using an antibody to Mac-1 to inhibit restenosis following vascular injury. An abstract published by Simon *et al.* in Circulation, Supp. 1, vol. 100, no. 18 November 2, 1999, number 1742 (attached as Exhibit 1), is submitted with this response demonstrating that an equivalent effect can be obtained with a peptide inhibitor.

This is in addition to the lengthy discussion in the application as originally filed which defines the integrins and ligands (page 7, lines 13-25; page 8, line 7 to page 9, line 10; page 9, line 22-page 10, line 11); the classes of compounds, including antibodies (page 9, lines 11-22; page 10, line 10-page 11, line 19); peptides and peptidomimetics (page 11, line 20, to page 13, line 19); methods for screening for compounds and generation of synthetic compounds randomly and by computer aided design (page 13, line 20 to page 16, line 15), and nucleic acid molecules (page 16, line 16, to page 19, last line). Carrier materials are described on page 20. Methods for administration are detailed at page 20, line 22, to page 22, line 2.

*c. The Examiner has provided only allegations; not support for his rejections*

No proper *prima facie* case for lack of enablement has been established. The Examiner has provided no evidence or convincing argument that the claimed method cannot be used for the *in vivo* purposes described in the specification. Rather, the Examiner has merely expressed the opinion that the claimed method is unpredictable. This clearly does not meet the standard to establish a *prima facie* case of lack of enablement.

The Examiner argued that the animal model studies in general relating to restenosis have not correlated well with clinical trial results in human patients, and that this in combination with the breadth of the claims to any compounds which would inhibit or reduce leukocyte-integrin-mediated adhesion, would mean that undue experimentation would be required to practice the claimed method. For some reason the examiner discusses the need for *in vivo* data to demonstrate that a therapy will be effective, but ignores the fact that the examples in the application as originally filed are in fact *in vivo* (although a rabbit rather than a human). There is also discussion about the fact that it takes years of development to prove a clinical treatment. The truth of this is indisputable but not relevant: the fact is that the applicants have provided *in vivo* evidence in their application showing that an antibody to at least one of the claimed integrins was effective in an animal model and in combination with independent third parties have provided evidence that another completely different kind of molecule, a peptide, derived from the integrin ligand glycolipid-anchored urokinase receptor, was also effective.

1. Animal Models are Predictive of Efficacy

The rejection is initially based on the proposition that the animal models, specifically the rat and rabbit animal models used by applicants, do not correlate well with *in vivo* clinical trial results. Enclosed in response are three papers and abstracts of two others (copies of which are attached as Exhibit 2). The abstract of Coats, et al., "Remodeling and restenosis: insights from animal studies" Semin. Interv. Cardiol. 2(3), 153-158 (1997), notes that animal studies in remodeling and its contribution to restenosis have been critical, and correlated with human studies. Farb., et al., "Pathology and Chronic Coronary Stenting in Humans," Circulation, 99:44-

52 (1999), paper notes at page 51, col. 2, that "These data in the pig model regarding inflammation and thrombus closely reflect the findings observed in human coronary stenting early after implantation (with a relatively longer duration of healing in humans)." The authors then note that there is a difference in the type of vascular injury in normal arteries of animals as compared to the response in human atherosclerotic arteries. (This may be one reason why there has been variable correlation with some reported models). Komatsu, et al., "Neointimal Tissue Response at Sites of Coronary Stenting in Humans" Circulation 98, 224-233 (1998), reports that animal models are generally predictive (page 230), with dogs being an exception (page 232). Kearney, et al., "Histopathology of In-Stent Restenosis in Patients with Peripheral Artery Disease", Circulation, 95:1998-2002 (1997) correlates results in humans obtained at autopsy with animal studies, beginning at the bottom of page 1999, col. 2. The abstract of Folts, et al., J. Am. Coll. Cardio. 33(2), 295-303 (1999), notes that an animal model, the cyclic flow model of coronary thrombosis, has been useful in predicting which agents are likely to be of benefit in clinical trials.

In summary, the literature supports the use of animal models as predictive of efficacy.

2. Data demonstrates Efficacy of Inhibiting Integrin-mediated Inhibition

Example 2, beginning on page 22 of the application, shows administration of an antibody to rabbits after arterial injury. The data demonstrated that there was a reduction in neointimal area after deep injury of nearly 40% relative to controls. This data alone indicates that the active agent can be effectively delivered. No adverse effects were noted.

Also provided to the examiner (in Exhibit 3) is an article by the authors and others which was submitted to the J. Clin. Invest. entitled "Decreased neointimal formation in Mac-1 (-/-) mice reveals a role for inflammation in vascular repair after angioplasty. (published by Simon, et al., J. Clin. Invest. 105(3), 293-300 (February 2000)). This paper describes the role of inflammation in mechanical arterial injury, in particular Mac-1, which when absent results in significantly less intimal proliferation and thickening after injury.

*3.* There are numerous protein therapies

The relevance of the comments regarding potential degradation of compound, etc. at pages 3-4 of the office action is not clear. Many pharmaceutical proteins and numerous antibodies are administered to patients as therapeutics, absent side effects, and without loss of function. For example, as shown by the abstract by Topol, et al., "Long-term protection from myocardial ischemic events in a randomized trial of brief integrin beta3 blockade with percutaneous coronary intervention. EPIC Investigator Group. Evaluation of Platelet IIb/IIIa Inhibition for Prevention of Ischemic Complication" JAMA 278(6):479-484 (1997). (Exhibit 4)

In view of the preceding arguments and the recent *Amgen* decision, Applicants assert that the specification clearly enables the claims directed to a compound to reduce or inhibit stenosis or restenosis after injury to vascular tissue. The requirements of 35. U.S.C. § 112, first paragraph (enablement) have been met.

**II.** Claims 1-9 and 11-12 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

*a. The legal standard*

The standard regarding what is or is not supported by the specification has been clearly articulated as requiring the specification to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, the inventor was in possession of the invention, i.e.,

whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 19 USPQ2d 1111, 1117 (Fed . Cir. 1991). Compliance with the written description requirement is essentially a fact-based inquiry that will "necessarily vary depending on the nature of the invention claimed." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) (citing *In re DiLeone*, 436 F.2d 1404, 1405 (CCPA 1971)). Essentially, satisfaction of the written description requirement is determined on a case-by-case basis.

The inquiry into adequate written description is not performed in a vacuum. "Knowledge of one skilled in the art is relevant to meeting [the written description] requirement." *Enzo Biochem, Inc. v. Gen-Probe*, Docket No. 01-1230 (Fed. Cir. Apr. 2, 2002) (slip op.). This fact has implications not only for validity challenges, but also for patent prosecution. *See In re Alton*, 76 F.3d 1168, 1174-75 (Fed. Cir. 1996).

It was recently clarified in Enzo Biochem that "the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure. See *Enzo Biochem*, 296 F.3d at 1324, 63 USPQ2d at 1613. Although it has been previously expected that all candidates of a genus be described in detail, a recent decision by the C.A.F.C., stated that "the specification's description of producing the claimed EPO in two species of vertebrate or mammalian cells adequately supports claims covering EPO made using the genus vertebrate or mammalian cells, [and] renders Eli Lilly listless in this case." *Amgen*, 126 F.Supp2d at 149, 57 USPQ2d at 1507. The C.A.F.C. has ruled that adequate description of one species satisfies the written description for the corresponding genus of compounds.

*b. The present claims satisfy the written description requirement*

The specification supports the use of any "compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function". Detailed description is provided for compounds such as antibodies or antibody fragments (p9-11), peptide and peptidomimetic compounds (p11-p13) and nucleic acid regulators (p16-19) that inhibit or reduce leukocyte integrin-mediated adhesion or function. These compounds share the common feature that they all bind integrins or their ligands. One of skill in the art would be aware of compounds and the mechanisms that they act on the integrins. The Examples of the specification describe in clear detail how one would use a "compound" (in this case Mac-1) to reduce or inhibit leukocyte integrin-mediated adhesion or function. Computer assisted drug design is described on page 15 wherein one can model drugs and their interactions with the integrins. This method describes a concrete method by which one can come into possession of a wide range of compounds that reduce or inhibit integrin-mediated adhesion or function. The Examples of the specification describe in detail and demonstrate reduction to practice of one such compound. As stated in the recent CAFC decision, adequate description of claims to species support the claims to the genus. In this case, several species have been described in detail in the specification. The legal standard is met.

The elected invention of anti-Mac-1 antibodies including soluble adhesion molecules and adhesion molecule-specific antibodies as well as the fibrinogen peptide discussed in the specification including the full breadth of the claimed "compounds", meets the written description provision of 35 U.S.C. 112, first paragraph.

**Rejection Under 35 U.S.C. § 102**

Claims 1-10 were rejected under 35 U.S.C. § 102(b) as being anticipated by Simon et al., Circulation 92, 8 Suppl: I-110 Abstract 0519 (1995) ("Simon"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claims 1-12 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,976,532 to Coller and Knight ("Coller"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claims 1-12 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,210,671 B1 to Co et al. ("Co"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claims 1-10 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,840,793 to Todd et al., ("Todd"). Applicants respectfully traverse this rejection.

*a. The Legal Standard*

For a rejection of claims to be properly founded under 35 USC §102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); *Scripps Clinic & Research Found v Genentech Inc*, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed

invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

[A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to practice the invention. The Federal Circuit held that "a §102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. . . [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *Paperless Accounting Inc v Bay Area Rapid Transit Sys.*, 231 USPQ 649, 653 (Fed. Cir. 1986) (citations omitted).

Further to the issue of inherency, "[a]nticipation is a question of fact, as is the question of inherency. *In re Schreiber*, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997). Its proof differs from that for obviousness, 35 U.S.C. §103, in that prior knowledge by others requires that all of the elements and limitations of the claimed subject matter must be expressly or inherently described in a single prior art reference. *In re Robertson*, 169 F.3d 743, 745, 49

USPQ2d 1949, 1950 (Fed. Cir. 1999); *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1571, 7 USPQ2d 1057, 1064 (Fed. Cir. 1988). The single reference must describe and enable the claimed invention, including all claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the filed of the invention. *Crown Operations International, Ltd. V. Solutia Inc.*, 289 F.3d 1367, 1375, 62 USPQ2d 1917, 1921 (Fed. Cir. 2002); *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ("the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the filed of the invention in possession of it.")

When anticipation is based on inherency of limitations not expressly disclosed in the assertedly anticipating reference, it must be shown that the undisclosed information was known to be present in the subject matter of the reference. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749-50 (Fed. Cir. 1991) Inherency cannot be based on the knowledge of the inventor; facts asserted to be inherent in the prior art must be shown by evidence from the prior art. *Cf. In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999)

*b. The Prior Art*

The claims are drawn to "an effective amount of a compound specifically inhibiting or reducing leukocyte adhesion or function mediated by an integrin, to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue.

*i.* *Simon, et al. (Circulation)*

Simon, et al., (Circulation) reports on studies using an antibody fragment c7E3 immunoreactive with platelet glycoprotein IIb/IIa. The abstract reports that the antibody was effective at reducing **"ischemic complications"** six months after coronary angioplasty and clinical restenosis. The abstract also reports that the antibody is cross-reactive with Mac-1.

The 7E3 antibody is known to inhibit integrin binding in cell culture, and be very effective in treating thrombotic conditions. However, treatment of thrombotic complications (i.e., ischemia and ischemia-reperfusion injury) is not the same as, nor predictive of, treatment of patients to prevent or reduce restenosis. The abstract does not report treatment of patients, the dosages, the times of administration nor indeed is that the focus of the abstract. The abstract reports *in vitro* studies that identify the activity of the antibody as cross-reactive with Mac-1 as well as platelet glycoprotein IIb/IIa. The patent describes treatment of a different class of patients, at different administration times and dosages.

Thrombolysis causes injury due to a disruption in blood flow, followed by reperfusion, where the endothelium is intact.

Restenosis is injury arising when there is disruption in the endothelium while the blood flow remains continuous. Restenosis involves recruitment of platelets and leukocytes. As shown by abstract, Mickelson, et al., "Chimeric 7E3 Fab (ReoPro) decreases detectable CD11b on neutrophils from patients undergoing coronary angioplasty", J. Am. Coll. Cardiol. 33(1):97-106 (1999), (Exhibit 5), this antibody decreases detectable CD11b on neutrophils but does not bind to neutrophils nor inhibit adhesion, two of the major factors involved in restenosis. See also

Deitch, et al., "Effects of beta3-integrin blockade (c7E3) on the response to angioplasty and intra-arterial stenting in atherosclerotic nonhuman primates", Arterioscler. Thromb. Vasc. Biol. 18(11):1730-7 (1998 Nov). As further shown by the paper, The Eraser Investigators, "Acute Platelet Inhibition with Abciximab Does Not Reduce In-Stent Restenosis (ERASER Study), Circulation 100:799-806 (1999) (Exhibit 5), this antibody did not inhibit restenosis. This evidence demonstrates that antibody 7E3 does not inhibit restenosis and therefore Simon, et al. does not anticipate the claimed method.

*ii.* *Coller, et al.*

Coller et al., describes the 7E3 antibody which is discussed by Simon, et al., (Circulation). The patent reports that the antibody is specific for glycoprotein IIb/IIIa and can be used as an antithrombotic agent. There is no disclosure of the use of the antibody to inhibit or prevent restenosis. As discussed above, the 7E3 antibody does not inhibit restenosis.

The evidence demonstrates that this antibody ("7E3" or "Reopro") does not affect restenosis and that this is not an inherent property of the antibody. Therefore Coller, et al. does not disclose the claimed subject matter.

*iii.* *Co*

Co describes the use of humanized immunoglobulins in the treatment of ischemic-reperfusion injury. Co teaches that angioplasty is a method of preventing restenosis. Co teaches administration of antibodies in combination with thrombolytic or angioplastic treatment, not in place of it. The present claims are directed to reducing stenosis/ restenosis after injury by administering one compound that specifically inhibits or reduces leukocyte integrin-mediated

adhesion. As Co does not disclose the same method defined in the present claims, the present method is not anticipated.

*iv.* *Todd, III, et al.*

Todd teaches reduction of tissue damage at a site of inflammation after myocardial infarct, ischemic-reperfusion injury or angioplasty. Todd teaches antibodies to decrease the inflammatory response and infarct size, not decrease cell adhesion or stenosis/restenosis. Todd teaches that occlusion causes myocardial infarct in an experimental canine model for myocardial infarct. One of ordinary skill would have to 'envisage' many features absent teachings in the instant specification to practice the claimed method. As Todd does not disclose each and every claim limitation, Todd does not anticipate the present claims.

**Rejection Under 35 U.S.C. § 103**

Claims 1-12 were rejected under 35 U.S.C. § 103 as being unpatentable over Simon et al. *Circulation* 92, 8 Suppl: I-110 Abstract 0519 (1995) ("Simon"), in view of U.S. Patent No. 5,976,532 to Coller and Knight ("Coller") and/or U.S. Patent No. 4,840,793 to Todd et al ("Todd") and/or U.S. Patent No. 6,210,671 B1 to Co ("Co"). Applicants respectfully traverse this rejection.

*a.* *Simon et al.*

Simon is discussed above. Simon does not describe an antibody that inhibits restenosis.

*b.* *Coller et al..*

Coller is discussed above. Coller does not describe an antibody that inhibits restenosis.

*c.* *Co*

Co is described above. Co does not teach using a single agent to inhibit or reduce stenosis or restenosis after injury.

*d.* *Todd, III, et al.*

Todd is described above. Todd does not teach use of antibodies to inhibit or reduce stenosis or restenosis after injury.

*e.* *There is no motivation to combine the references*

It has been made very clear that "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Further, the "level of skill in the art cannot be relied upon to provide the suggestion to combine references. Al-site Corp v. VSI Int'l Inc., 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication. In this case, there is no teaching in the prior art that would suggest combining the references, and the Applicants have also achieved unexpected results.

*f. Applicants have attained unexpected results*

Efforts at limiting the undesirable proliferative and disease states of vascular endothelium have focused on the isolated administration of analogs of endothelial compounds. Certain drugs, such as heparin, are especially effective inhibitors of vascular smooth muscle cell proliferation in tissue culture and animal models of arterial diseases precisely because they mimic the activity of natural endothelial-derived compounds like heparan sulfate proteoglycan, Edelman, E.R. & Karnovskv, M.J. *Circ.* 89: 770-776 (1994). However, despite cell culture and small animal data supporting the regulatory role of heparin-like compounds, exogenous heparin preparations have shown no benefit in human trials. Non-heparin endothelial compounds such as nitric oxide and the prostaglandins are potent regulators of a range of biologic effects involving smooth muscle cells. Inhibitors of these compounds have been shown to control intimal hyperplasia following experimental vascular injury (Cooke et al., *Curr. Opin. Cardiol.*, *7*: 799-804 (1992); Moncada et al., *N. Engl. J. Med.*, *329*: 2002-2012 (1993); McNamara, et al., *Biochem. Biophys. Res. Comm.*, *193*: 291-296 (1993)). This is indicative that the vascular endothelium is a powerful regulator of the blood vessel wall, not because of the production and secretion of one compound alone, but because of its presence as an intact unit.

One skilled in the art would not expect only a single compound to be effective in limiting or preventing restenosis. This is demonstrated by Co et al. where antibodies are administered in combination with thrombolytic agents or angioplasty. The results obtained by appellants showing that a single class of compound, compounds blocking binding and activation of certain integrins, could effectively limit restenosis were completely unexpected. Importantly, it is not

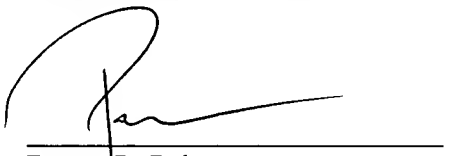
administration of a single compound, but class of compounds, that achieves this effect. These compounds inhibit or reduce leukocyte adhesion or function by interference with integrin-mediated binding.

**Double Patenting Rejection**

Claims 1-12 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of co-pending U.S. Patent Application Serial No. 08/823,999. This issue has been deferred in view of the impending decision in the parent application.

Allowance of claims 1-12 is respectfully solicited.

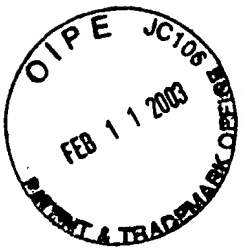
Respectfully submitted,



Patrea L. Pabst
Reg. No. 31,284

Date: February 6, 2003

HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8473
(404) 817-8588 (Fax)




## Clean Version of Amended Claims
## Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. A method of inhibiting or reducing stenosis or restenosis of a blood vessel following injury to vascular tissue in a region of the blood vessel of a patient in need of treatment thereof, comprising:

administering systemically or at the site of the injury a pharmaceutically acceptable composition comprising a compound which specifically inhibits or reduces leukocyte integrin-mediated adhesion or function in an amount effective to inhibit or reduce stenosis or dependent restenosis of a blood vessel following injury to vascular tissue.

2. The method of claim 1 wherein the leukocytes are monocytes or granulocytes.

3. The method of claim 1 wherein the injury arises from angioplasty, atherectomy, endovascular stenting, coronary artery bypass surgery, peripheral bypass surgery, or transplantation of cells, tissue or organs.

4. The method of claim 1 wherein the composition is in a form selected from the group consisting of solutions, gels, foams, suspensions, polymeric carriers, and liposomes.

5. The method of claim 1 wherein the integrin is selected from the group consisting of Mac-1, LFA-1, p150,95, and CD11d/CD18.

6. The method of claim 5 wherein the integrin is Mac-1.

7. The method of claim 6 wherein the ligand is selected from the group consisting of ICAM-1, fibrin(ogen), C3bi, and factor X.

8. The method of claim 1 wherein the compound is selected from the group consisting of antibodies and antibody fragments that are immunoreactive with integrins or their ligands and which block the interaction of the integrins or their ligands with vascular cells; molecules which inhibit expression of the integrins or their ligands, and peptides and peptidomimetics derived from the integrins or their ligands which block the interaction of the integrins or their ligands with vascular cells or tissues.

9. The method of claim 5 wherein the integrin is LFA-1 and the ligand is selected from the group consisting of ICAM-1, ICAM-2, ICAM-3.

10. The method of claim 6 wherein the compound is an antibody or antibody fragment immunoreactive with Mac-1.

11. The method of claim 1 wherein the compound is administered to a patient in need thereof prior to vascular intervention.

12. The method of claim 11 wherein the compound is administered to a the patient prior to and after vascular intervention, until healing has occurred.

**Marked Up Version of Amended Specification Paragraphs**

**Pursuant to 37 C.F.R. § 1.121(b)(1)(iii)**

Please replace the paragraph on page 11, lines 10-19, with the following paragraph.

--These antibodies can be further modified by the use of [Pharmacia's] PHARMACIA'S® ([Pharmacia] PHARMACIA® LKB Biotechnology, Sweden) "Recombinant Phage Antibody System" (RPAS), which generates a single-chain Fv fragment (ScFv) which incorporates the complete antigen-binding domain of the antibody. In the RPAS, antibody variable heavy and light chain genes are separately amplified from the hybridoma mRNA and cloned into an expression vector. The heavy and light chain domains are co-expressed on the same polypeptide chain after joining with a short linker DNA which codes for a flexible peptide. This assembly generates a single-chain Fv fragment (ScFv) which incorporates the complete antigen-binding domain of the antibody.--

Please replace the paragraph on page 12, lines 13-16, with the following paragraph.

--The peptides can also be conjugated to a carrier protein such as keyhole limpet hemocyanin by its N-terminal cysteine by standard procedures such as the commercial [imject] IMJECT® kit from Pierce Chemicals or expressed as a fusion protein, which may have increased efficacy. --

Please replace the paragraph on page 15, lines 20-25, with the following paragraph.

--Examples of molecular modeling systems are the CHARMm® and QUANTA® programs, Polygen Corporation, Waltham, MA. CHARMm® performs the energy minimization and molecular dynamics functions. QUANTA® performs the construction, graphic modeling and analysis of molecular structure. QUANTA® allows interactive construction, modification, visualization, and analysis of the behavior of molecules with each other.--

Please replace the paragraph on page 19, lines 13-26, with the following paragraph.

--Methods to produce or synthesize oligonucleotides are well known in the art. Such methods can range from standard enzymatic digestion followed by nucleotide fragment isolation (see e.g., Sambrook et al., Chapters 5, 6) to purely synthetic methods, for example, by the cyanoethyl phosphoramidite method using a Milligen or [Beckman] BECKMAN® System 1Plus DNA synthesizer (see also, Ikuta et al., in *An. Rev. Biochem.* 1984 53, 323-356 (phosphotriester and phosphite-triester methods); Narang et al., in *Methods Enzymol.,* 65, 610-620 (1980) (phosphotriester method). Accordingly, DNA sequences of the 5' flanking region of the integrin protein gene described herein can be used to design and construct oligonucleotides including a DNA sequence consisting essentially of at least 10 to 15 consecutive nucleotides, with or without base modifications or intercalating agent derivatives, for use in forming triple helices specifically within the 5' flanking region of a integrin protein gene in order to inhibit expression of the gene.--

Please replace the paragraph on page 20, lines 8-16, with the following paragraph.

--Carrier materials for direct administration include biodegradable materials, such as a synthetic polymer degrading by hydrolysis, for example, polyhydroxy acids like polylactic acid, polyglycolic acid and copolymers thereof, polyorthoesters, polyanhydrides, proteins such as gelatin and collagen, or carbohydrates or polysaccharides such as cellulose and derivatized celluloses, chitosan, alginate, or combinations thereof. Other materials include block copolymers of polyoxyethylene ([Pluronics] PLURONICS® [™], BASF®) or the diacrylate block copolymers described by Hubbell, et al, in U.S. Patent No. 5,567,435 issued on October 22, 1996.--

Please replace the paragraph on page 20, lines 17-21, with the following paragraph.

--The use of biodegradable matrices eliminates the need for surgery to remove implanted materials. However, synthetic non-biodegradable matrices may also be used. Useful materials include ethylene vinyl acetate, polyvinyl alcohol, silicone, polyurethane, non-biodegradable polyesters, and tetrafluoroethylene meshes ([Teflon] TEFLON®).

Please replace the abstract of the application with the following paragraph.

-- Compounds that specifically inhibit or reduce leukocyte adhesion or function are useful to enhance vascular healing and lessen restenosis of blood vessels after revascularization, via angioplasty or bypass surgery, of diseased coronary, peripheral and cerebral arteries, and lessen stenosis or restenosis of surgically-placed bypass grafts and transplanted organs. Examples of these compounds are those which block cell surface integrins, such as Mac-1 (CD11b/CD18,

αMβ2) or their ligands[, for example, the leukocyte integrin Mac-1 (CD11b/CD18, αMβ2)]. [As demonstrated by the examples both] Both superficial and deep injury was significantly reduced with treatment using an antibody to Mac-1 compared to both saline controls and IgG controls in the examples. After balloon angioplasty (superficial injury) neointimal area was reduced nearly 70%. The ratio of intimal:medial area[, which is customarily used in balloon-injured experimental arteries to normalize for small normal variations in arterial size from one animal to another,] was reduced over 75%. After endovascular stent implantation (deep injury) neointimal area was reduced nearly 40%. Extrapolated to humans, this reduction in the intimal thickening would reduce occurrence of restenosis from [occurring in] approximately 30% of patients to less than 10% [of patients].--

ATL1 #561577 v1